REMARKS

Status of Claims

Claims 1-4, 6 and 7 are hereby amended to more particularly point out and distinctly claim that which applicants regard as their invention. No new matter is added by any of the amendments. Claims 1-4, 6, 7, 9-26 and 29 are presented for further examination.

The Presently Claimed Invention

The present invention relates to the discovery that tramadol and diclofenac form a sparingly soluble compound, such that when formulated together, these ingredients form a compound with a relatively low solubility. To address this problem, the present formulations provide the active ingredients in separate subunits, so that no sparingly soluble compound is formed and the active ingredients are released more quickly than if the active ingredients were mixed together. Providing these two particular active ingredients in separate subunits results in unexpected and unforeseen beneficial effect, in that the release of the active ingredients can proceed much faster than if the ingredients were mixed together during the formulation process. Accordingly, the presently claimed formulations allow the skilled artisan to achieve a release rate of tramadol and diclofenac from a single administration unit which corresponds to the release rate from administration units having only tramadol or diclofenac as the active ingredient (see, e.g. paragraph [0048] of the present application and Figures 1, 3 and 4).

The present inventors have discovered that tramadol hydrochloride and diclofenac sodium together form a sparingly soluble compound. As a result of the formation of this sparingly soluble compound, the bioavailability of the two active substances is reduced, and higher dosages are required in order to compensate for the impaired solubility (cf. specification, paragraph [0006]).

It was thus the object of the present invention to provide a new pharmaceutical dosage form for combined administration of tramadol and diclofenac (cf. specification, paragraph [0007]) which would combine the two active

substances tramadol and diclofenac and/or their respective physiologically compatible salts in a common administration unit without impairing the release profiles of the two active substances or reducing their bioavailability (cf. specification, paragraph [0008]). These objects are surprisingly both achieved by the presently claimed oral dosage form.

It has been found that the released amounts and the release profiles of tramadol and diclofenac from the oral administration unit according to the invention correspond to the amounts and release profiles from separate dosage forms containing in each case only tramadol or only diclofenac. This was surprising and unexpected for a person skilled in the art in view of the finding that tramadol hydrochloride and diclofenac sodium form a sparingly soluble compound and their expected reduced bioavailability as a result of this compound formation.

Rejections under 35 U.S.C. § 103(a)

The rejections of claims 1-4, 6, 7, 9-26 and 29 under 35 U.S.C. § 103(a) over the combination of Voss et al., 4,690,927; Mok et al., *Am. Soc. Clin. Pharmacol. and Ther.*, Feb. 1996, p. 132; Addicks et al., US 5,041,430; Bergamini et al., US 5,597,560 and Bodley et al., US 5,679,660 and over the combined disclosures of Raffa et al., US 5,516,803; Mok et al.; Addicks et al.; Bergamini et al. and Bodeley et al. are each respectfully traversed. There is nothing in any of the cited art which disclose or suggest not only the problems associated with combining tramadol and diclofenac as presently claimed, but also the unexpected benefits afforded by the present formulations.

Voss et al. relates to a combined dosage form of diclofenac-sodium and codeine, but is silent as to any unfavorable physical or chemical interaction between diclofenac and tramadol and does not disclose discrete subunits for the active ingredients. In all of the specific examples provided in Voss et al., the active agents are mixed together.

Raffa discloses a composition comprising a tramadol material and an NSAID. Raffa does not explicitly disclose the presently claimed combination of

tramadol or a pharmaceutically acceptable salt thereof with diclofenac or a pharmaceutically salt thereof. Moreover, Raffa, like Voss et al., provides no indication that there might be any problem arising from the direct combination of tramadol and diclofenac.

Mok et al. is newly cited as showing that simultaneous administration of tramadal (presumably tramadol) and diclofenac produced superior pain relief. However, Mok et al. does not add any new aspect to the prior art cited so far. Rather, Mok et al. relates to a study that evaluated the analgesic efficacy and safety of the combined use of tramadol and diclofenac. During the course of this study the patients received tramadol *IV* and diclofenac *IM*. The statement that tramadol was given *IV* (intravenously) means that a suitable solution comprising tramadol was introduced directly into a vein. The statement that diclofenac was given *IM* (intramuscularly) means that a suitable solution comprising diclofenac was injected directly into a muscle. Thus, the two active agents were administered separately by entirely different routes of administration. Indeed, neither tramadol, nor diclofenac was administered orally. Therefore Mok et al. teaches nothing about how to formulate an oral dosage form of tramadol and diclofenac, much less anything about how to prevent formation of a sparingly soluble compound that reduces the bioavailability of the two active substances.

As noted, according to Mok et al., tramadol and diclofenac were given via different routes of administration, namely intravenously and intramuscularly. Consequently, these substances were necessarily administered to different parts of the human body and therefore could not form a sparingly soluble compound with one another. Such a situation is not in the least comparable to the administration of both compounds via one and the same oral dosage form. Rather, when an oral dosage form comprising both tramadol and diclofenac is administered, then both tramadol and diclofenac will be present in the gastroenteral tract, which could lead to the formation of sparingly soluble compound between these components. In other words the problem underlying the present invention cannot

occur during the study as described in the reference of Mok et al., and Mok et al. provides no help in solving it.

Addicks discloses a pharmaceutical dosage form comprising an anticoagulant, such as wafarin, and a platelet inhibiting agent, such as aspirin or some other NSAID, separated by a coating layer. However, Addicks, like Voss et al. and Raffa, does not evidence any awareness or appreciation of the formation of a release-inhibiting sparingly soluble compound by tramadol and diclofenac.

Bergamini and Bodley are cited as purportedly disclosing that diclofenac exhibits interaction with a number of active ingredients. However, Bergamini focuses on the combination of diclofenac with tobramycin and does not disclose tramadol, a completely different active ingredient. Bodley discloses the combination of diclofenac with 2-hydroxypropyl beta-cyclodextrin. Bodley also does not disclose the combination of tramadol and diclofenac. None of the references disclose the particular issues associated with the combination of diclofenac and tramadol, including the formulation of a compound with a relatively low solubility.

To summarize, neither of the primary references discloses that there would be any disadvantageous result in combining tramadol and diclofenac as mixed together in a single dosage form, much less suggests how to achieve a rapid release rate of tramadol and diclofenac from a combined dosage form. And none of the secondary references remedy the deficiencies of Voss et al. and Raffa. Consequently, the presently claimed oral administration unit is not rendered obvious by the combined disclosures of the cited prior art. Reconsideration and withdrawal of the rejections are accordingly, respectfully requested.

Conclusion

In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt, favorable action thereon is earnestly solicited.

If there are any questions regarding this Reply or the application in general, a telephone call to the undersigned at (202) 624-2845 would be appreciated since this should expedite the examination of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket No. 029310.50777CP).

Respectfully submitted,

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J. D. Evans
Registration No. 26,269

CROWELL & MORING LLP
Intellectual Property Group
P.O. Box 14300
Washington, DC 20044-4300
Telephone No.: (202) 624-2500
Facsimile No.: (202) 628-8844
JDE/moi *(doc. #13418116)*